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Clinical utility trial incorporating biomarkers into a risk model for lung cancer screening

S.Hanash

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20 Year Journey

What have we done

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20 Year Journey

What have we done

Where are we at

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20 Year Journey

What have we done

Where are we at

Where do we go from here

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Disclosures

- IP/Invention disclosures filed for pan-cancer, lung cancer, pancreatic cancer, colon cancer, ovarian cancer and prostate cancer biomarkers and for therapeutic targets
- *IP licensed to Thrive (now Exact Sciences), Dynex, Cosmos, OncImmune*
- Consultant to: Abbott, Abbvie, BMS, Takeda

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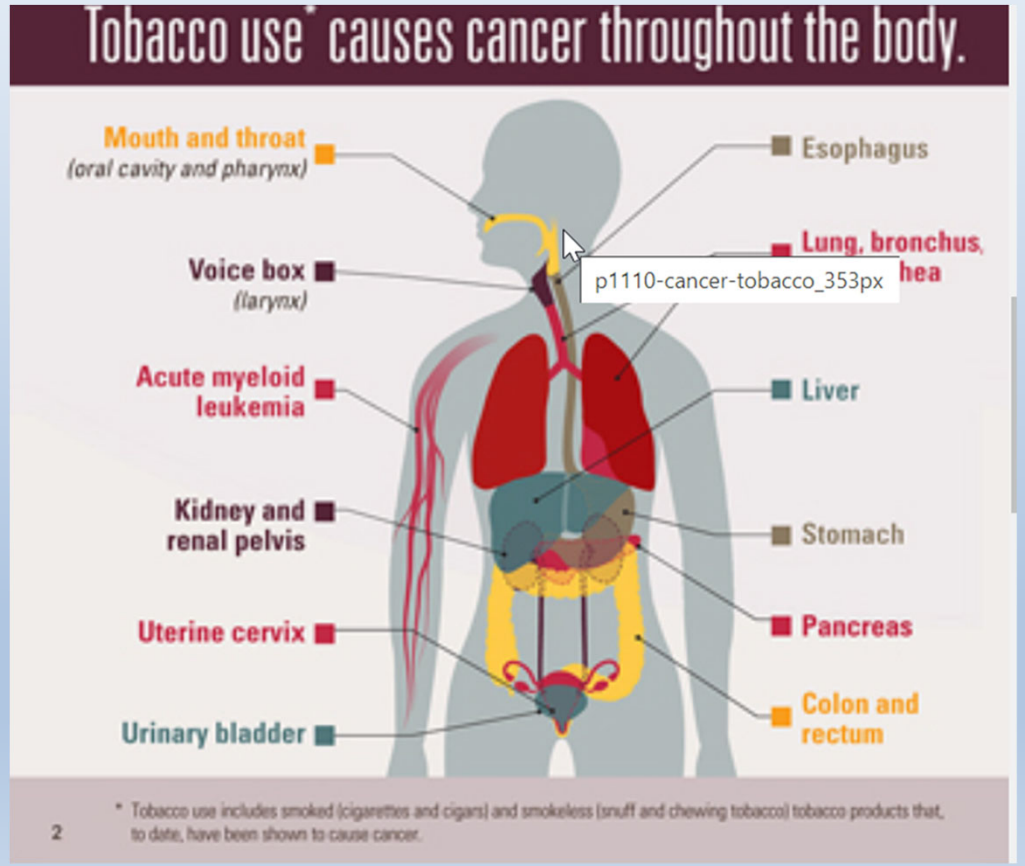
Why a utility trial for lung cancer

- #1 cancer killer
- Smokers are at increased risk for other diseases, cancers
- A utility trial for lung cancer provides an opportunity for validation of pan-cancer markers



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Lung cancer screening recommendations

- Current USPSTF: Annual low-dose CT for smokers with at least 30 pack-years and no more than 15 years since quitting, ages 55-80 (*CMS: ages 55-77, shared-decision making*)
- New 2020 USPSTF draft recommendations: reduce pack-years to 20 and age to 50, quit < 15 years
- Still leave out a good percentage of subjects destined to be diagnosed with lung cancer

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Potential benefits of personalized risk assessment

- Bring to screening subjects that don't meet eligibility criteria but have a personalized risk equivalent to risk for eligible subjects so as to catch more lung cancers early
- Reduce screening needs for subjects that meet eligibility criteria but have a reduced personalized risk
- Contribute to assessment of indeterminate nodules
- Increase uptake of CT screening

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NEW RESEARCH IN Physical Sciences Social Sciences Biological Sciences

RESEARCH ARTICLE

An immune response manifested by the common occurrence of annexins I and II autoantibodies and high circulating levels of IL-6 in lung cancer

Franck M. Brichory, David E. Misek, Anne-Marie Yim, Melissa C. Krause, Thomas J. Giordano, David G. Beer, and Samir M. Hanash

PNAS August 14, 2001 98 (17) 9824-9829; https://doi.org/10.1073/pnas.171320598

> 70 papers to date

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Discovery and validation of ProSFTPB as anchor marker for early detection of lung cancer

- Discovery based on proteomics applied to animal models of lung cancer and subjects with early stage lung cancer led to the discovery of ProSFTPB (Cancer Cell 2011)

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- Validation of ProSFTPB in pre-diagnostic samples from the CARET and PanCan cohorts (JCO 2013) and the Harvard PHS cohort (CEBP 2013)

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- Validation of ProSFTPB in pre-diagnostic samples from the CARET and PanCan cohorts (JCO 2013) and the Harvard PHS cohort (CEBP 2013)
- Validation of the combination of ProSFTPB + DAS in CARET cohort (JCO 2015)

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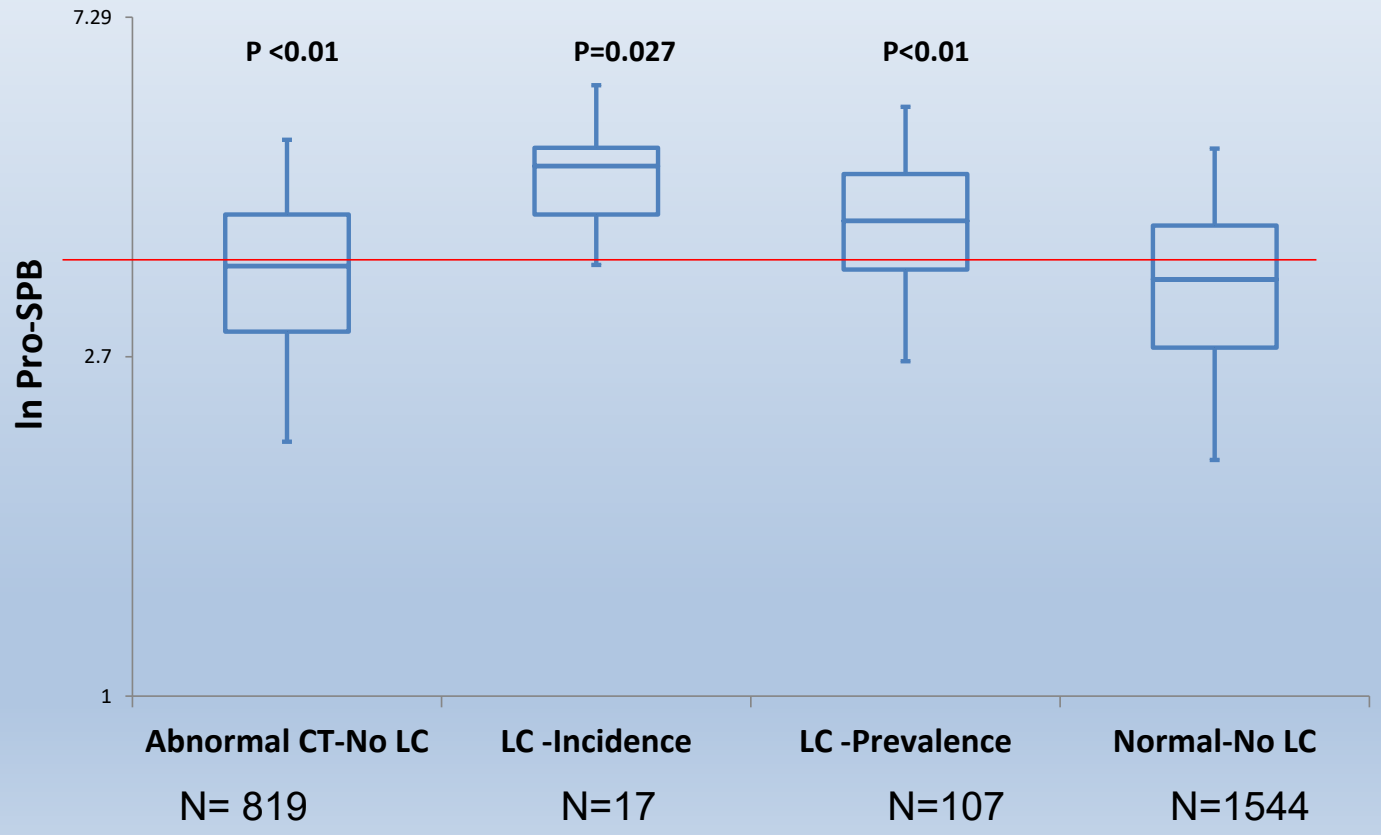
Pro-Surfactant Protein B Identifies Incident Lung Cancers



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Road map

- > 10,000 lung cancer biomarker papers
- Pick out initial marker type(s)/platform(s)
- Consider analytical variability, practicality, cost effectiveness of biomarker combinations

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Search for biomarkers with potential utility for lung cancer screening

- Nucleic acids:
    - Mutated DNA
    - Non-coding RNA
- Metabolites
- Immune related:
    - Cytokines/chemokines
    - Autoantibodies
- Circulating microparticles/exosomes

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MD Anderson miRNA candidate list

- 74 with at least one publication for early detection
- 20 with at least two publications for early detection(+)
- 25 (‡) consistently over-expressed in IPAS (across 42 Lung Cancer cell lines), including 7 with more than 1 Early Detection publication, 12 with only 1 Early Detection publication(‡), and 6 not related to Early Detection (‡)
- 8/25 consistently over-expressed in IPAS LC cell lines also in Sozzi's list
- Other considerations:
  - Overlap miRNAs across three independent review analyses (10 miRNAs)
  - Sozzi's miRNAs (24 miRNAs) (•)
  - Rosetta Genomics miRNAs for tumor differentiation (†)

miR-21•‡†+, miR-210+, miR-205†, miR-145•+, miR-182, miR-101•, miR-375†, miR-31‡, miR-203, miR-16•,miR-17•‡+, miR-486-5p•+, miR-126•+, miR-140-5p•+, miR142-3p•+, miR-148a•+, miR-30b•‡+, miR-30c•‡+, miR-92a•‡+, miR106a•‡†, miR-133a•, miR-140-3p•, miR-15b•‡+, miR-197•, miR-19b•, miR-221•‡+, miR-28-3p•+, miR-320•+, miR-451•+, miR-660•+, miR-125a-5p†‡, miR-129-3p†, miR-29b†, miR-7† *(34 miRNAs)*

Potential Additional miRNAs:

Let-7a‡, mir-20a‡, miR-24‡, miR-29a‡, let-7b‡, miR-103‡, miR-222‡, miR-30a‡, miR-139-5p‡, miR-26a‡, miR-27b‡, miR-125b‡, let-7f‡, miR-34a‡, miR-23a‡

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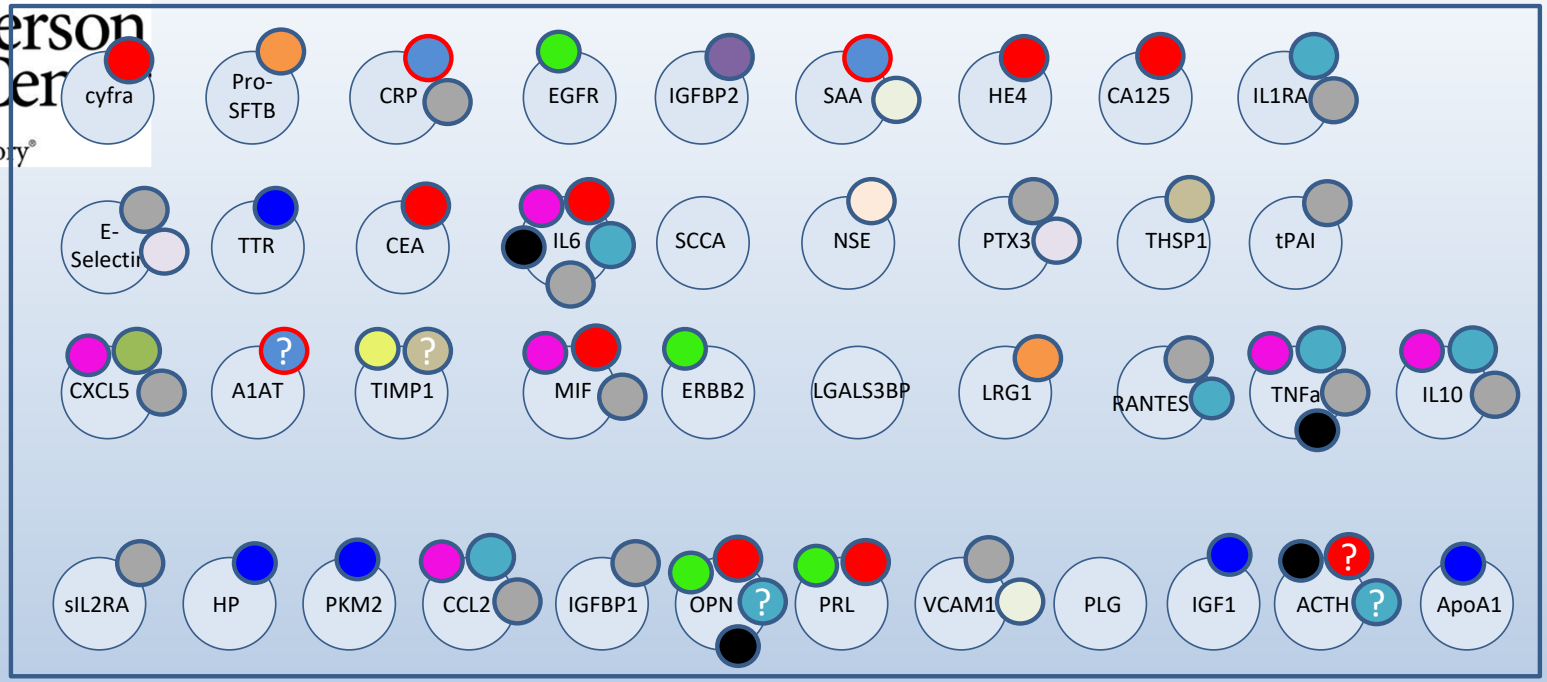
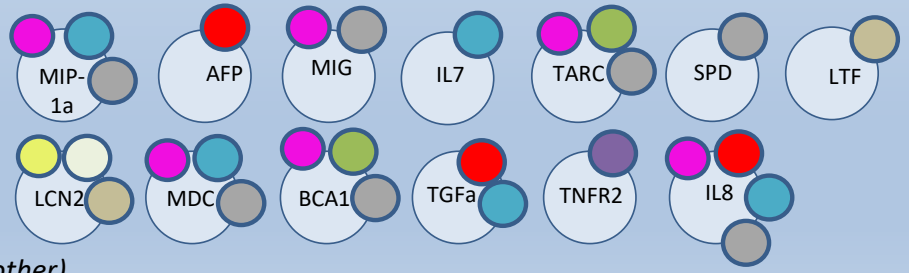


Additional relevant proteins that could be added with no sample volume "cost" due to their presence in commercial panels



Singleplex or other panel (not related to each other)

In-house
HCCBP1MAG-58K
Millipore 1
HSP3MAG-63K
Millipore 2
HCYTOMAG-60K
HND1MAG-39K
HCYTOMAG-62K
R&D screen
Bio-Rad LZ0000D2DTE31D
HCVD2MAG-67K
HCVD4MAG-67K
Bio-Rad LH000001VR
HKI5MAG-99K
HBNMAG-62K

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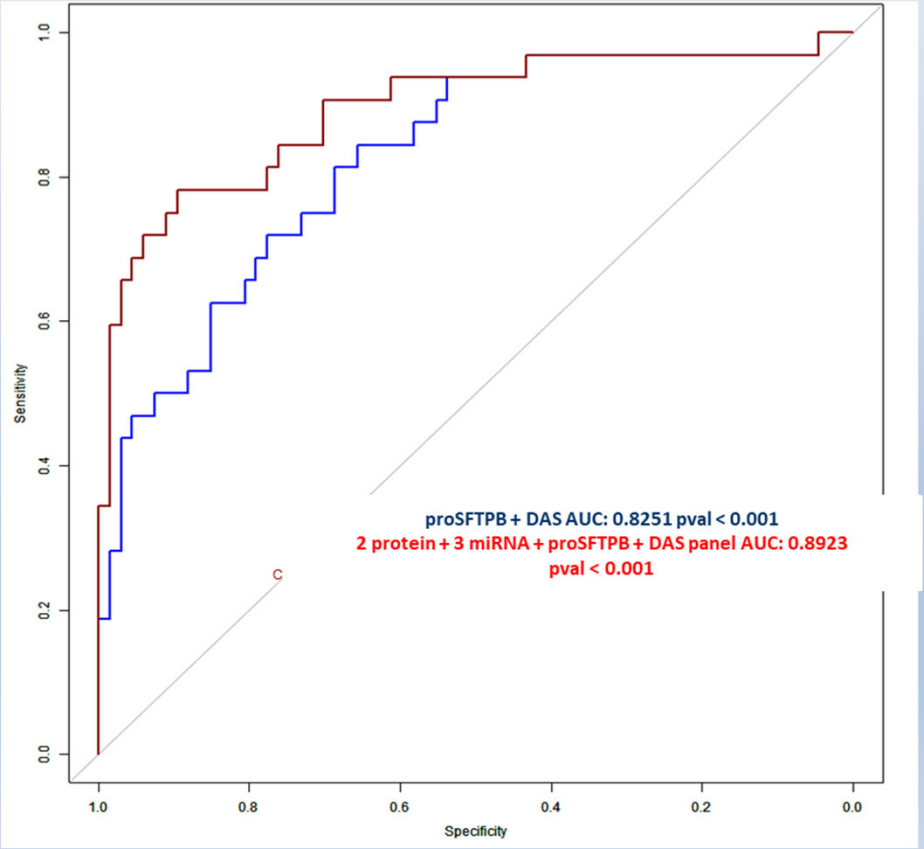
Example of performance of markers from more than one platform based on pre-diagnostic CARET Cohort



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Development of a 4-marker panel for early detection of lung cancer

- Extensive validation of ProSFTPB justified considering ProSFTPB as anchor marker for lung cancer screening
- A total of an additional 50 marker candidates were tested in the CARET cohort that resulted in a 4-marker panel (4MP = ProSFTPB, CEA, CA125, CYFRA21)
- 4MP validated in the European Northern Sweden and EPIC Cohorts (Guida et al JAMA Oncol 2018)

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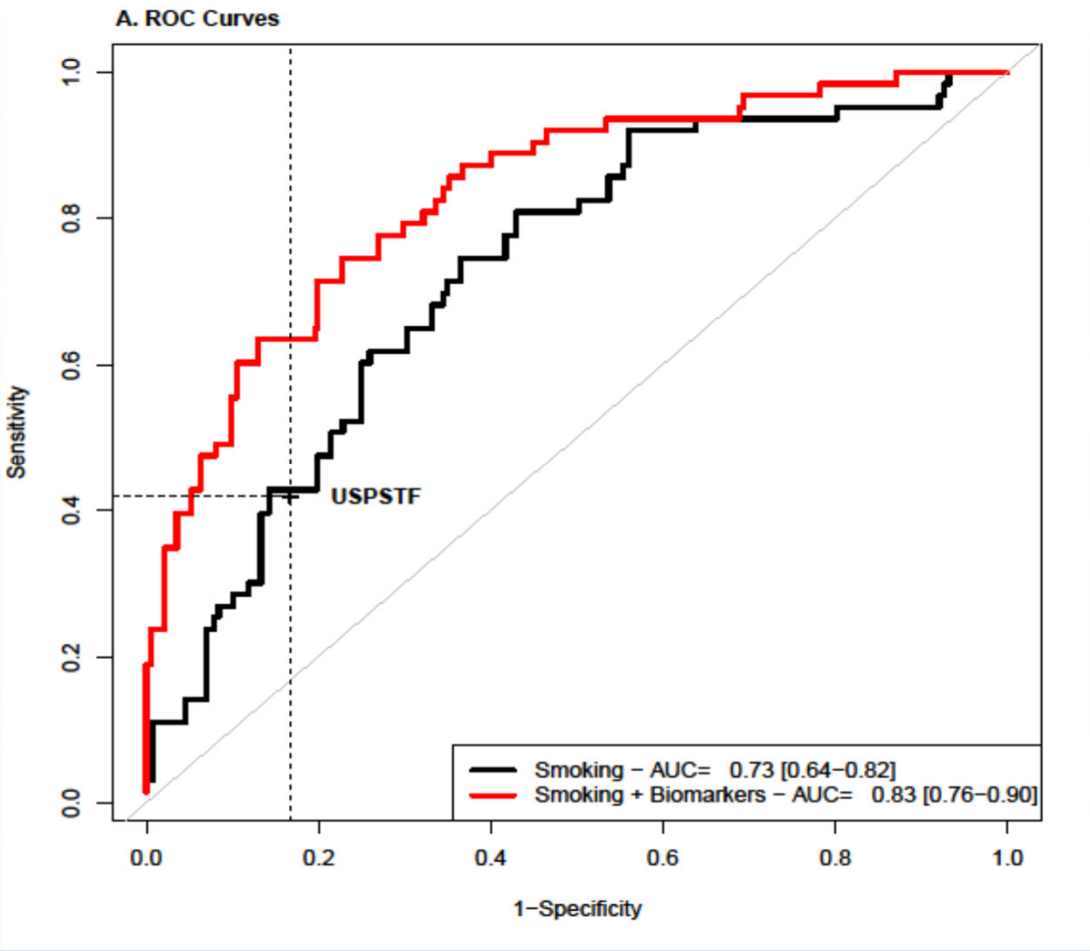

ROC curve analysis in the validation study (EPIC and NSHDS ever smoker subjects diagnosed within 1 year of blood collection) for two risk prediction models, smoking variables only, and an integrated model with the smoking variables and the biomarker score combined.

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PLCO validation study

Based on combination of:

4-protein marker panel (4MP)

+

Lung cancer risk model (PLCO 2012)

(Tammemagi M etal NEJM 2013)

FPZ5

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PLCO Validation Study

- Ziding Feng and Tracey Marsh *Fred Hutch*
- Martin Tammemagi *Brock University*
- Stephen Lam *UBC*
- Rafael Meza *U of Michigan*
- Margaret Spitz *Baylor*
- Sanjay Shete *MDA*

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FPZ5 You did not list Tracey!
Feng PhD, Ziding, 10/24/2020

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PLCO Cohort Validation Study

- Ed Ostrin
- Johannes Fahrmann
- Ehsan Irajizad
- Jody Vykokal
- Jennifer Dennison
- Nikul Patel

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PLCO Cohort

Total samples tested	# of cases (within 5 years of time to DX)	# of controls
10605	**1299**	**8746**

Time to DX: [0-1)	All cases	Adenocarcinoma	Squamous	Small cell
	370	152	82	51

Markers Tested:
ProSFTPB, CEA, CA125, CYFRA21

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Development of decision rule based on 4MP+PLCO 2012

Blinded training set with fixed 4MP combination rule

Total samples tested	Number of Cases	Number of Controls
4554	**538**	**3764**

Time to DX: [0-1) : # of Cases: 152
# of Controls: 3764

Blinded Validation with decision rule

Total samples tested	Number of Cases	Number of Controls
6051	**761**	**4945**

Time to DX: [0-1) : # of Cases: 218
# of Controls: 4945

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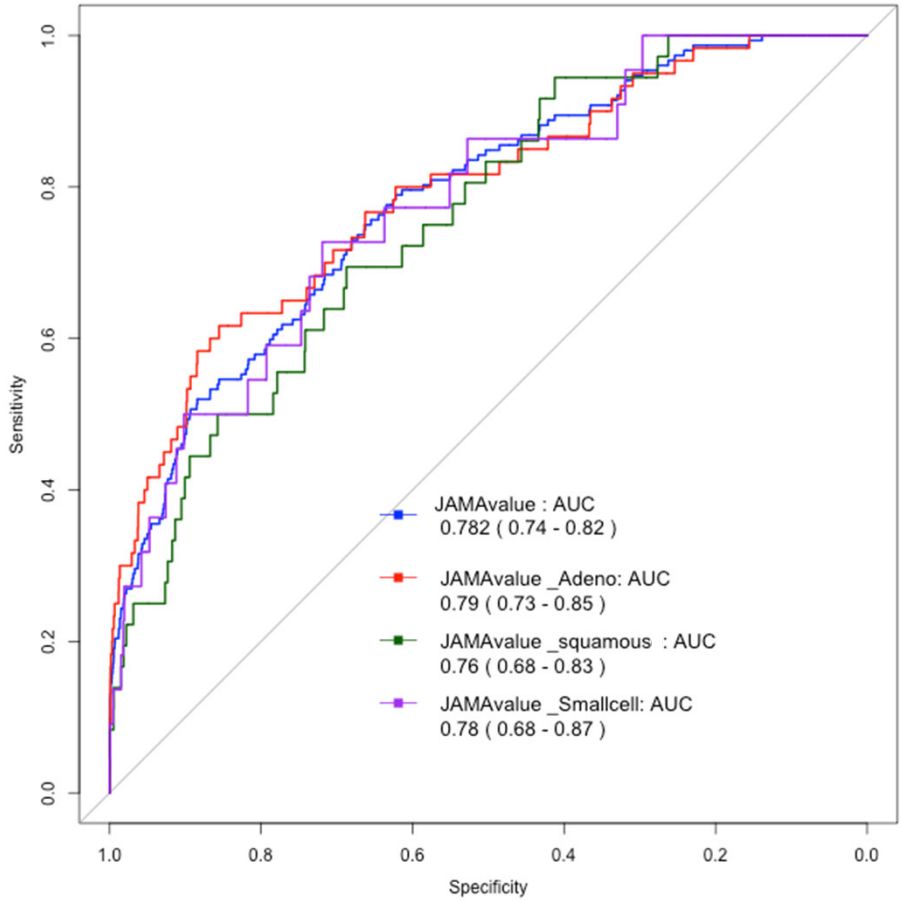
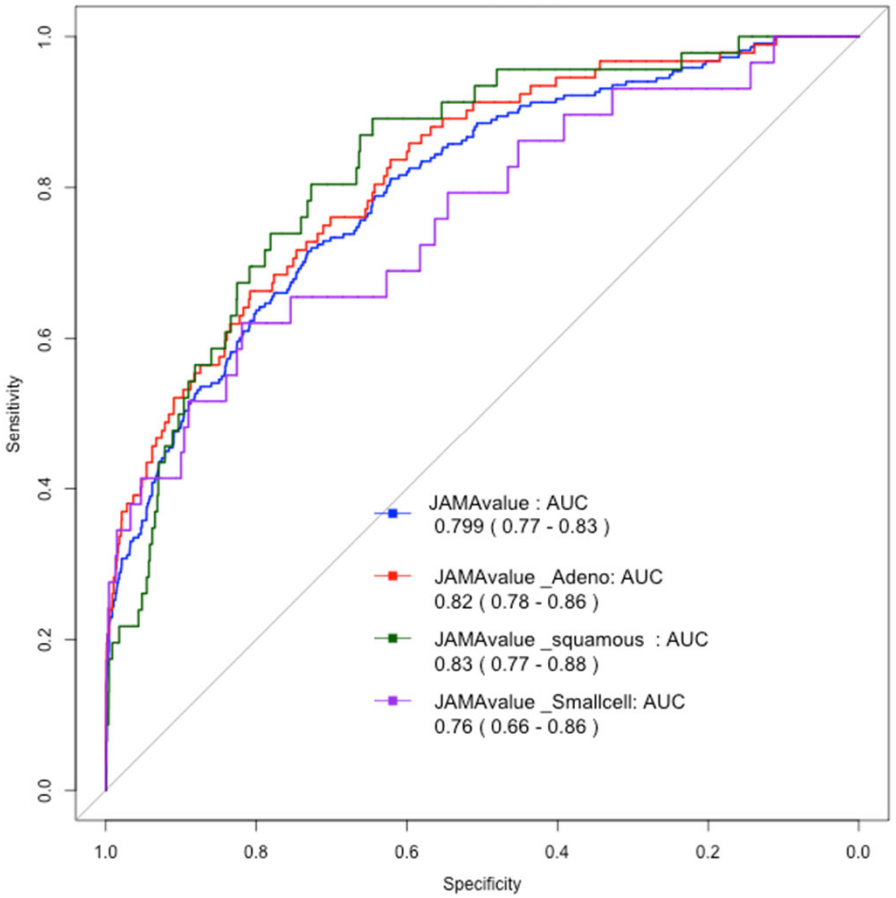
PLCO Cohort – 4MP panel

Training



Validation



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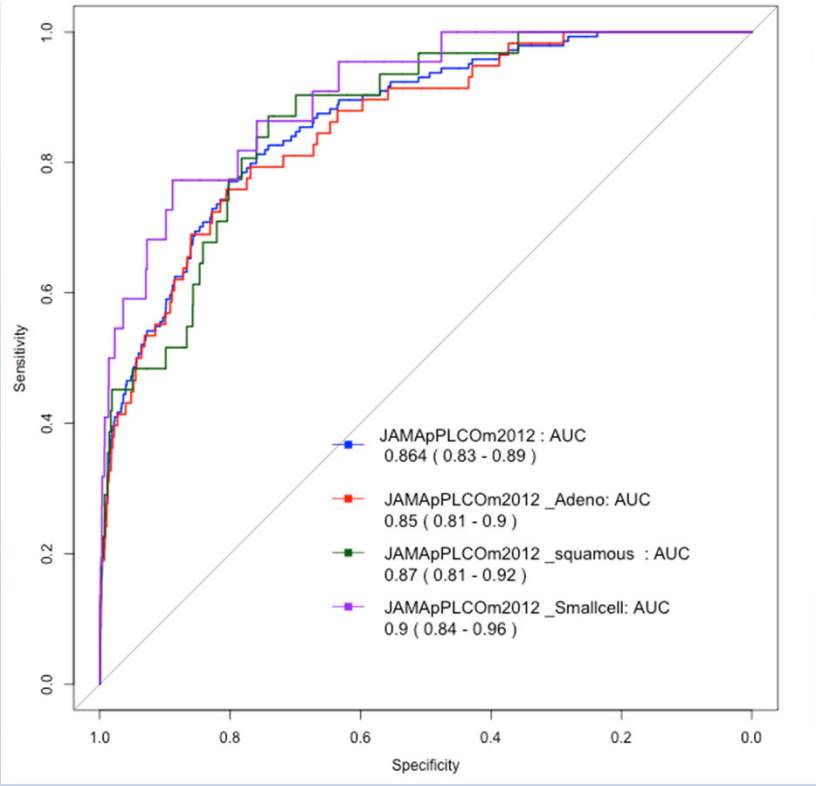
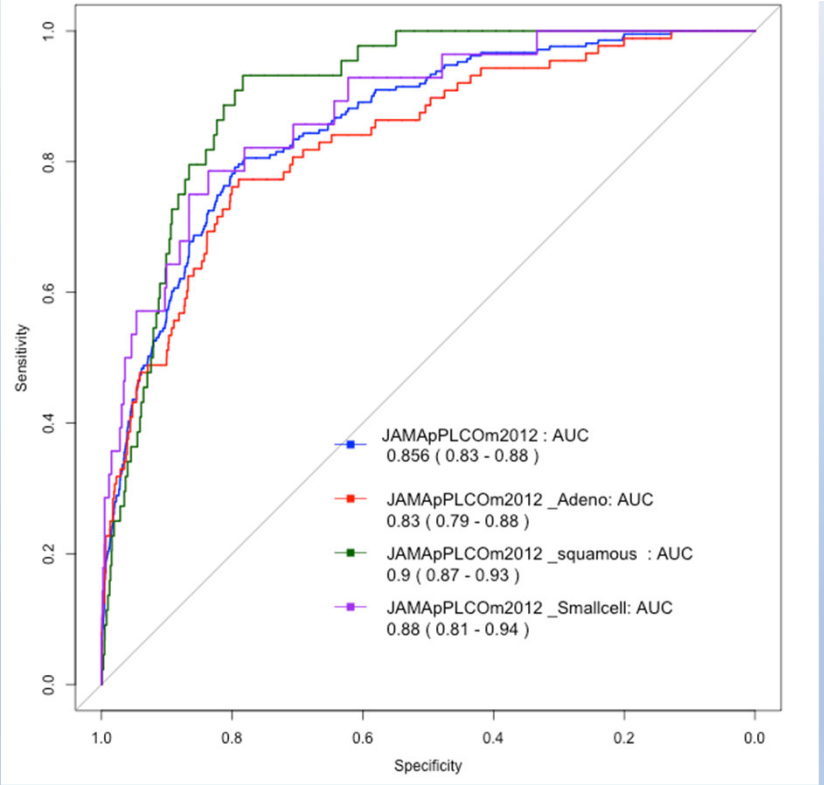
PLCO Cohort – 4MP + PLCOm2012

Training



Validation



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Lung risk groups based on smoking criteria
(+ = eligible based on USPSTF criteria)

Criteria	Analysis	TF2013	TF2020
<10py	-	-	-
10-20py	Low	-	-
20-29py;>=15qy	Low	-	-
20-29py;<15qy	Med	-	+
30+py;>=15qy	Med	-	-
30+py;<15qy	High	+	+

USPSTF Criteria: Current (TF2013) and recent draft (TF2020)

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4MP + PLCOm2012 (1% risk)

strata	AUC	sens	spec	PPV	NPV
Low	0.794	0.500	0.906	0.029	0.997
Med	0.778	0.682	0.611	0.033	0.990
High	0.817	0.986	0.269	0.047	0.998
All	0.842	0.884	0.562	0.043	0.995

FPZ3

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FPZ3 The 0.01% should be 1%, the 6-yr risk of 1.0%.

Feng PhD, Ziding, 10/24/2020

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4MP + PLCOm2012 (1.7% risk)

strata	AUC	sens	spec	PPV	NPV
Low	0.794	0.438	0.956	0.053	0.997
Med	0.778	0.614	0.775	0.051	0.990
High	0.817	0.944	0.445	0.058	0.995
All	0.842	0.835	0.693	0.057	0.995

FPZ4

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FPZ4 again should be 0.017, not 0.017%

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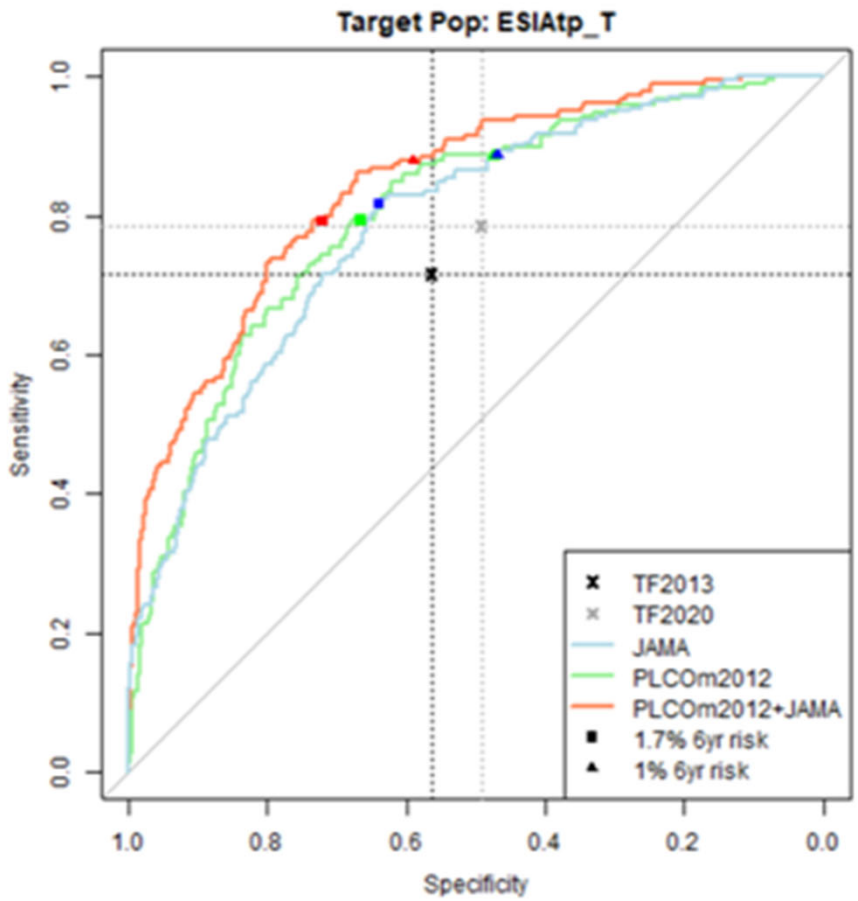
4MP+PLCOm2012 vs TF



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Clinical utility trial incorporating biomarkers into a risk model for lung cancer screening

- **Trial concept**: An intervention trial to compare sensitivity and specificity of biomarker driven decision rule vs that of TF2020 guideline
- **Hypothesis**: A risk model driven intervention (at threshold of 6-yr risk 1.0%) will have higher sensitivity (sensitivity at 12m follow up) and better specificity than that by TF2020
- **Study outcome**: Lung cancer within 12 m of enrollment
- **Study endpoint**: comparison of sensitivity and specificity of risk model vs TF2020

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Clinical utility trial incorporating biomarkers into a risk model for lung cancer screening

Eligibility:

- 10+ py smokers currently not eligible but that meet a 6 y risk threshold of 1% based on 4MP + PLCO 2012 will undergo LDCT N= 14,000
- *Most currently eligible subjects do not undergo LDCT screening.* Currently eligible subjects undecided re LDCT will be informed of their risk based on 4MP + PLCO 2012 will be informed of their risk through shared decision making N=7,000
- Currently eligible subjects that undergo LDCT N=7,000 (MDACC Leap Study already recruited > 8,000 subjects in this group)

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Study requirements

- Baseline + one year blood collection
- Baseline + one year LDCT (for current risk group)
- Follow-up: three years from baseline
- Management of positive subjects according to current guidelines

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FPZ2 Red text means that they are not required to answer the primary hypothesis of the trial, thus they are optional for debate

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Secondary objectives

- Screening uptake rate (proportion of guideline eligible who did not plan to take screening LDCT at baseline who ended up taking screening LDCT within 12m from baseline
- Contribution of subject risk + nodule characteristics to assessment of indeterminate nodules *(Ostrin E et al JTO in press)*
- Biospecimen repository for testing other promising markers for lung cancer or for pan-cancer

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Power calculations

- Model sensitivity 88% vs TF2020 sensitivity 80%
- Model specificity 58% vs TF2020 specificity 51%
- 28,000 enrolled, 90% power
- Distribution of enrolled represents the distribution of 10+ PY smokers in US (~50% eligible, ~50% ineligible)
- 8,000 enrolled in Leap Study potentially relevant

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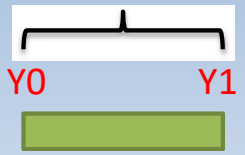
LEAP Participating Sites

- MD Anderson – Houston, TX
- US Cancer Network Sites (AL,FL,OH,NJ,TX)
- USC
- Stanford
- Sister Institutions in Europe (Madrid, Paris)
- Sister Institutions in China (Anhui, Henan, Xuzhou)

Site Visits
LDCT, Blood, Questionnaire



FPZ1

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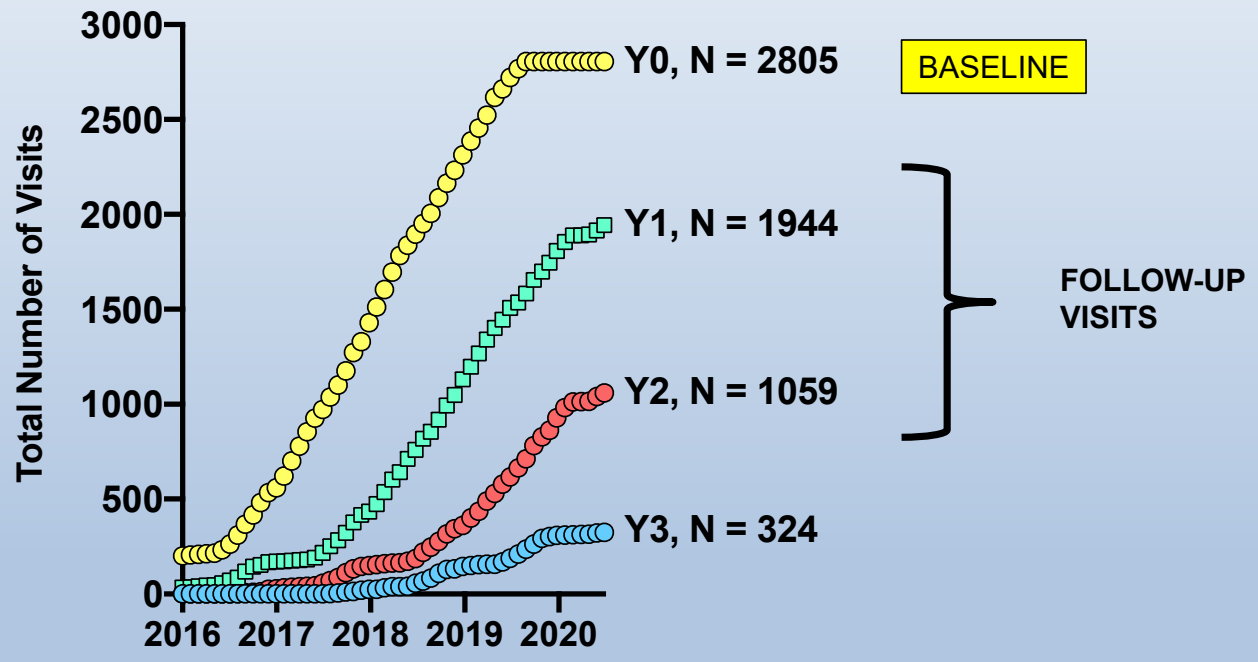
LEAP – US & European Sites
Total Number of Visits



5706 blood specimens (280,000 aliquots)
50 lung cancers, 55 other cancers

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FPZ1 Why not present # from China?

Feng PhD, Ziding, 10/24/2020

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- **Lung Cancer Collaborators:** L. Bantis,, P. Brennan, A, G. Calin, K. Do, Z. Feng, O. Fiehn, D. Gandara, A. Gazdar, F. Guida, G. Goodman, M. Johansson, S. Lam. M. H. Levine, R. Meza, V. Nair, E. Ostrin, F. Perera, R. Prentice, A. Rundle, H. Sesso, S. Shete, M. Spitz, M. Tammemagi, M. Thornquist, H. Varmus, D. Wilson, I. Wistuba, H. Ying, J. Yuan,

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EPIC	*NCI UO1*
PLCO	*NCI UO1, NCI SCLC Consortium*

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Discussion items

- Should we have a non-intervention control arm?
- Is year one LDCT a requirement or subject follow-up is enough?
- Merits of expanding trial to outside US eg Canada, Europe, China and Australia ?

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Launch of **ACED**

Association for Cancer Early Detection